Fighting Food Allergy by Inducing Oral Tolerance: Facts and Fiction

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Abstract
The prevalence of food allergy (FA) is increasing, and there is an urgent need to take effective measures against it. One important measure is the avoidance diet, which shows a disadvantage, especially in case of accidental exposure. Oral tolerance restoration sheds new light on the control of FA. Oral tolerance is naturally a state of systemic unresponsiveness of the gastrointestinal tract to food antigens and its restoration can be a clinical therapy for FA. Its immune basis lies on the intestinal mucosal immune system and factors, such as gut microbiota and food processing methods, are also important. This review presents recent advances in oral tolerance and its closely related factors.

Introduction

Food allergy (FA) is an adverse reaction to certain foods or food additives that are harmless to unsusceptible individuals. The response can be immunoglobulin E (IgE)-mediated (type I hypersensitivity) or non-IgE-mediated (type IV hypersensitivity), and the former is the most common type. Allergic reactions often occur in the skin, digestive system, or respiratory system, and there can be systematic and even life-threatening symptoms [1]. Oral food challenge results, which were published in the recent 5 years presented that, in developed countries, 3.8–11\% of children had FA [2–4]; however, for adults, the prevalence was from 0.2 to 4.1\% [5, 6]. The occurrence of FA in developing countries is comparatively lower, with about 0.5–2.5\% prevalence among children [7, 8]. To make it worse, the incidence of FA seems to be increasing over the past 20 years [9, 10]. On the other hand, epidemiological data showed that the types of food allergens responsible for eliciting FA vary among different continents. In Europe, United Kingdom, Australia, Canada, and the USA, peanuts are one of the main causes of FA [11–15]. While peanut allergy is not so common in many countries in Asia [16, 17], milk and eggs are the common allergenic foods among infants and young children of all countries [11, 18–20].

Till date, there are no well-accepted measures for the treatment of FA, and specific food elimination diet is the recommended choice. However, strict food avoidance can lead to poor adherence or malnutrition, and the risk of serious allergic reactions may increase when certain allergenic foods are accidentally ingested after a long-term

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avoidance. Thus, effective therapies against FA are urgently needed. So far, oral immunotherapy proposed in clinical and related experimental studies has become a potential preventive agent and an effective method against some FA. The ultimate goal of oral immunotherapy is to induce clinical tolerance, a state of restored permanent oral tolerance that is defined as no allergic response during oral food challenge after withdrawal of the antigen therapy, so that elimination diet can be stopped [21].

FA is fundamentally a state of loss of oral tolerance to food. After certain allergenic protein ingestion, it confronts denaturation and degradation in the digestive tract. However, a small fraction of the intact molecule or part of the protein (epitope) escapes from the digest process and comes to the intestinal cavity and intestinal mucosa. Then, it crosses the epithelial barrier through various mechanisms, gets help from specific types of epithelial cells, such as antigen-sampling microfold cells and goblet cells, and is then transferred to dendritic cells (DCs) for presentation [22]. Antigen presentation is the basis for FA. Gut microbiome and T cell also play important roles in oral tolerance/FA induction and maintenance. In addition, food processing methods may affect how allergenic proteins are digested or transferred, thus making certain food edible for allergic individuals. Moreover, the immune-modulatory effect of processed foods has also been reported. This review focuses on oral tolerance and its related factors, including intestinal mucosal immune defense, intestinal microbiome, and food processing methods.

**Oral Tolerance**

In 1911, Wells and Osborne [23] demonstrated that guinea pigs did not develop an allergic reaction to corn or oat protein, which are part of their diet. The state of immunological unresponsiveness to food antigens ingested is called oral tolerance [24]. It is different from the immune deficiency or the inhibition state caused by receiving an immunosuppressive agent since responses are still triggered by other antigens. One of the key events for the break of oral tolerance to food sensitization is Treg reprogramming to Th2, and higher IgE level promotes Th2 cell induction and further inhibits Treg [25, 26]. Evidence also suggests that IgG4, in relation to IgE, is more accurate in terms of FA diagnosis when compared with specific IgE alone [27]. In recent years, FA research focused on infants and young children in early oral tolerance induction since “allergen avoidance strategy” is obviously not suitable for the control of allergic reactions [28]. For instance, by adding or avoiding peanut extract in 640 targeting infants until 5 years old, Du Toit et al. [29] reported that early consumption of peanut can significantly reduce the frequency of peanut allergy from occurrence of 13.7% in the exclusion group to 1.9% in the consumption group. Moreover, the peanut consumption group had higher ratios of peanut-specific IgG4/IgE, which indicates an immune-modulatory effect.

For many patients who were already allergic to certain foods, restoration of specific oral tolerance was proven to be a good treatment. For certain types of FA, such as milk and egg allergy, most of the cases present allergic reactions before 1 year of age and the majority of them outgrow FA before school age. However, for some other types, such as peanut and treenut allergy, it is more difficult to restore oral tolerance. A more detailed description for natural history of FA in different food types has recently been reviewed [30]. Immunological changes in restored oral tolerance involve an increase in specific IgG4 and Treg levels, as well as a reduced Th2 response [31–33]. Clinically, its basic strategy is to reduce adverse reactions to allergic food proteins by repeated exposure to gradually increasing doses. Fifty milk allergy subjects (median 10.3 years) participated in a 3-stage oral tolerance restoration test. The whole procedure lasted for 67 days, beginning with one drop of 1% milk solution, and ending with 250 mL of milk. Results showed that 23 patients achieved full tolerance, 9 patients achieved partial tolerance, and 18 patients failed to achieve tolerance. The achieved clinical tolerance lasted for at least 5 years [34]. In an egg tolerance restoration test, 20 patients (5–11 years) were randomly divided into treatment and control groups. The treatment group followed a dosage increase protocol, starting with 1 drop of raw hen egg and ending at 176 days with 40 mL of raw hen egg (a dose equivalent to a small egg). After 6 months, 9/10 children in the treatment group achieved partial tolerance and 1 child was not tolerant. No oral tolerance was achieved in the control group [35]. Although specific oral tolerance restoration was effective in many clinical trials, long-term efficacy to sustain the achieved tolerance and uniformed protocol is still on the way [36].

**Intestinal Mucosal Immune Basis for Oral Tolerance**

Sensitivity to food allergens begins with the absorption of antigens by the gut and the main route of exposure to food ingredients is through the gastrointestinal...
mucosal surface. Gastrointestinal mucosa is the largest immune area in the human body, which distinguishes between beneficial and harmful components in the intestinal tract, so as to maintain systemic immune tolerance. Physically, the components of the intestinal mucosal immune defense can be divided into 3 different parts: intestinal epithelial barrier, lamina propria (LP), and gut-associated lymphoid tissue. Functionally, the intestinal mucosal immune defense system can be divided into induction sites and effector sites. The induction sites, which comprise isolated lymphoid follicles, mesenteric lymph nodes (MLN), and Peyer’s patches (PPs), are the places where antigens activate naive and memory T lymphocytes. The effector site where effector cells perform their action is composed of epithelial cells and LP [37]. According to the information (amount, size, shape, etc.) on the antigen entering the body, different parts of the mucosal tissue can be involved in oral tolerance induction. Among them, the vellus LP and MLN are the common induction sites of oral tolerance, and PPs may play a subordinate role [38]. The intestinal mucosal immune system and its role in processing food allergens are shown in Figure 1.

The initial structure of PPs (Anlagen) in human, which contains aggregates of T lymphocyte and some B lymphocyte, can be distinguished in 14-week-old fetuses [39]. Later and before puberty, the number and size of PPs increase with age. Dysplasia of MLN or PPs is consistent with reduced slgA and oral tolerance, thereby increasing susceptibility to infection and FA [40]. Besides, oral tolerance failed to be induced in both MLN- and PPs-deficient mice [41]. Intestinal epithelial cell also contributes to the maintenance of oral tolerance [42]. Lymphocytes called intraepithelial lymphocytes, which are scattered among epithelial cells, make contact with intestinal antigens directly and function as immune defense front against invading pathogens [43]. Together, these cells form an immune barrier in the intestinal tract, which is essential for a balanced intestinal mucosal immune system [44]. Without their matching, the intestinal immune system self-destructs, causing inability to induce protective immunity and/or tolerance, thus further leading to diseases, such as FA [45, 46].

DCs, which are partly located throughout the gut, are vital for T-cell activation and antigen presentation to B cell, and the mechanism of oral tolerance is related to the recognition of food antigens by DCs [47, 48]. Moreover, antigen-specific immunotherapy was found to induce tolerogenic DC in patients with FA [49]. Intestinal DCs contain both CD103+ and CD103− subsets. In LP, both CX3CR1+ macrophages and CD103+DCs are necessary for mucosal immunity. Generally, the abundant CX-
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after antigenic stimulation can be divided into 3 groups: degranulation inhibition, and Tregs induced in periphery by various mechanisms, such as Th2 cells, IgE, and effector cells that suppress induction and effector stages of FA through various mechanisms. Treg cells can play a significant role in FA and maintenance of tolerance. Treg cells can be divided into both IFN-γ and IL-17-producing effector T cells [53].

**T Cell and Oral Tolerance**

According to different CD molecular phenotypes, initial T cells can be divided into CD3+CD4+CD8− T cells (CD4+ T cell) and CD3+CD4+CD8+ T (CD8+ T cell) cells. When stimulated by a specific antigen after presentation, the initial CD4+ T cells can differentiate into cells, such as Th1, Th2, Th17, or Treg, which are important for FA [54]. It has long been accepted that pathogenic mechanisms of FA involve the skew of antigen-specific T-cell responses to Th2 [55–57]. Injection of mAb to pro-Th2 cytokines IL-25, IL-33, or thymic stromal lymphopoietin was found to strongly inhibit FA development in Balb/c mice. Moreover, injection of 3-mAb cocktail in the immunization process induced egg white tolerance [58]. Th2 to Th1 response shift and increase in Treg were found to be associated with long-term tolerance in clinical trials [59].

Many studies have shown that Tregs play an important role in FA and maintenance of tolerance. Treg cells can suppress induction and effector stages of FA through various mechanisms, such as Th2 cells, IgE, and effector cells that degranulate and inhibit, and Tregs induced in periphery after antigenic stimulation can be divided into 3 groups: Foxp3+Treg cells, TGF-expressing Th3 cells, and CD4+Foxp3-IL-10-producing Treg (Tr1) cells [60]. By treating FA mice models with a low dose of IL-2, Foxp3+Treg increase and activation were found to reduce clinical manifestations of FA. In Treg-depleted mice, no such effect was proven, thus indicating the central role of Treg in FA inhibition caused by low dose of IL-2 [61]. Kim et al. [62] demonstrated the immunosuppressive effect of Foxp3+Treg through common diet, which helps to establish oral tolerance. Although research in this field mainly involved animal experiments, clinically, there is also evidence that patients with restored oral tolerance have higher Foxp3+Treg level when compared with those with FA [63, 64]. Since a recent review [65] addressed Foxp3+Treg and oral tolerance in detail, we will not unfold the scroll here.

Th3 cell is a different type of peripheral regulatory CD4+ T cells, which primarily secretes TGF-β, an important mediator for oral tolerance induction [66]. In 30 children with multiple FA, dominant mucosal abnormality was found not to be skewed to Th2, but impaired the generation of Th3 cells, indicating the importance of Th3 in FA [67]. When fed a TGF-β-enriched formula to mice with ovalbumin (OVA)-induced FA, allergic responses were decreased when compared with the control group. IgE, IgG1, mMCP-1, and correlated cytokine levels all indicated decreased allergic responses [68]. Carrier et al. [69] found that Th3 cells can act directly and induce Foxp3+ to act indirectly as the central mediator of peripheral immune tolerance using a transgenic mouse model of TGF-mice. There are evidences that TGF-enriched formula helps infants to build oral tolerance [70]. However, although many reports found a relationship between TGF-β, FA, and oral tolerance, the clinical conclusion is still controversial [71].

In 1997, Groux et al. [72] first described Tr1, a regulatory T cell that can induce autocrine IL-10 and suppress CD4+ T-cell proliferation in response to antigen. In addition to its effect on CD4+ T cells, IL-10 also promotes antigen-presenting cells to induce the production of inhibitory T cells. Tsuji et al. [73] found that IL-10 secreted by Tr1 could induce tolerance to low levels of beta-globulin in mice. Bergerson et al. [74] isolated peripheral mononuclear cells from pediatric patients and found that children with FA have lower Tr1 levels when compared with those not allergic. Knol et al. [75] studied the T-cell clones from peripheral blood of children with persistent milk allergy, outgrown milk allergy, and without allergy. Results showed a Th2 skewed response in samples from persistent milk allergy subjects, while the milk-tolerant group presented higher levels of IL-10, indicating that the cytokine might contribute to FA tolerance induction. IL-10 agonists were found to have an immune regulatory effect on cancer patients [76], but whether this therapy can be used for FA patients with food-induced anaphylaxis is yet to be determined. The role of T-cells in induction of oral tolerance is shown in Figure 2.
Gut Microbiota and Oral Tolerance

The intestine is exposed to microbes as early as the fetus passes through the birth canal during delivery, and it may contain as many as 100 trillion microbes by adulthood. The gut, like other tissues, is constantly attacked by various antigens. Antigens come from the outside as well as the body itself. Recent data have shown that intestinal flora plays an important role in host immune development and function [77–79]. The increased prevalence of FA over the past few decades has increased concerns about the intestinal microbiota associated with allergies and oral tolerance promotion. In fact, epidemiological studies have demonstrated that intestinal microbiota plays an important role in early induction and maintenance of tolerance; moreover, altered microbial exposure and early life colonization were found to alter the risk of FA [80–82]. The effect of microbiota in allergy and oral tolerance was further confirmed with sterile mice. Rodriguez et al. [83] reported that, compared with normal mice, sterile mice are more likely to have allergic reactions after oral administration of whey proteins. When microbiota are transplanted from healthy infants (faecal microbiota dominated by Bifidobacterium and Bacteroides species), a protective impact of FA and increased expression of Foxp3 gene in the ileum was shown, indicating that the gut microbiota is closely associated with FA and oral tolerance [84].

For infants and young children, postnatal breastfeeding is particularly important in view of early induction of oral tolerance. Breastfeeding can transfer microorganisms to infants and affect the composition of intestinal microbiota of children, since breast milk is a source of nutrients for symbiotic microorganisms, such as bifidobacteria, lactobacillus, staphylococcus, and enterococcus [85]. In a 12-month longitudinal study, breastfed infants were found to receive 27.7% of breast milk bacteria and 10.3% of areola skin bacteria in the first month of life [86]. The latest Canadian longitudinal development of healthy infants prospective study found that both increase in richness of intestinal microbiota and low Enterobacteraceae/Bacteroidaceae ratio at 3 months of age could reduce the risk of food sensitization at 1 year old, which is related to breastfeeding [87]. Even after the introduction of solid foods, changes in bacterial diversity and composition were reported to be dose-dependently related with daily breast milk intake [86].

In addition to breastfeeding, timing to introduce solid foods that contain food allergen was also proven to affect oral tolerance induction. Many observational studies published in recent years support the idea that solid food introduction before 6 months of age could lower the risk of allergy to certain foods [88, 89]. A possible explanation might be the age-dependent relationship between infant gut microbiome and allergy. This was supported by Azad.
Table 1. Reported food processing measures that help patients tolerate processed foods in clinical trials [94, 97, 98, 100, 102, 105, 106, 117–131]

<table>
<thead>
<tr>
<th>Food</th>
<th>Cooking method</th>
<th>Rate of tolerance, % (n/N)</th>
<th>Age of population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>Sponge cooked at 177°C for 30 min</td>
<td>63 (59/94)</td>
<td>0.5–18 years old, median 4.25 years</td>
<td>Saifi et al. [97]</td>
</tr>
<tr>
<td>Oral food challenge in steps: (1) ciambellone with egg; (2) frittata (fried for 3 min and then baked at 180°C for at least 30 min); (3) egg boiled for 10 min (containing 6 g of egg protein)</td>
<td>88 (44/50) tolerated ciambellone, 74 (31/42) tolerated frittata, and 56 (28/50) tolerated boiled egg</td>
<td>0.5–16 years old, median 1.78 years</td>
<td>Miceli Soap et al. [98]</td>
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<tr>
<td>Muffin baked at 176°C for 30 min, or waffle at 260°C for 3 min (containing 2.2 g of egg protein)</td>
<td>55 (64/117)</td>
<td>1.6–18.6 years old, median 6.9 years</td>
<td>Lemon-Mulé et al. [102]</td>
<td></td>
</tr>
<tr>
<td>Cake (how much egg protein it contained not mentioned)</td>
<td>73 (44/60)</td>
<td>Children &gt;5 years old</td>
<td>Des Roches et al. [117]</td>
<td></td>
</tr>
<tr>
<td>Pasteurized liquid egg proceeded in the following steps: (1) stir-heated at 65°C for 10 min, (2) hydrolyzed with Protamex at 55°C for 2 h, (3) stir-heated at 75°C for 10 min, (4) hydrolyzed with Flavourzyme at 55°C for 2 h, and (5) stir-heated at 90°C for 30 min (containing 2.96 g of egg protein)</td>
<td>92 (22/24)</td>
<td>0.2–37.1 years old</td>
<td>Ballmer-Weber et al. [118]</td>
<td></td>
</tr>
<tr>
<td>Muffin baked at 176°C for 30 min, or waffle at 260°C for 3 min (containing 2.2 g of egg protein)</td>
<td>71 (56/79)</td>
<td>1.6–15.8 years old, median 5.8 years</td>
<td>Leonard et al. [100]</td>
<td></td>
</tr>
<tr>
<td>Muffin or cupcake baked at 176°C for 30 min (containing 2.2 g of egg protein)</td>
<td>84 (142/169)</td>
<td>1.48–17.07 years old, median 6.18 years</td>
<td>Bartnikas et al. [119]</td>
<td></td>
</tr>
<tr>
<td>Muffin baked at 180°C for 20 min (containing about 1 g of egg protein)</td>
<td>64 (150/236)</td>
<td>2.1–6.8 years old, median 4.5 years</td>
<td>Turner et al. [120]</td>
<td></td>
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<tr>
<td>Thirty-one of 34 patients were challenged with a boxed cake baked at 176°C for at least 30 min (containing 19 g of egg protein). The other 3 patients ingested baked cookies, donuts, or bread</td>
<td>82 (28/34)</td>
<td>1.2–13.8 years old, median 5.9 years</td>
<td>Buelow et al. [121]</td>
<td></td>
</tr>
<tr>
<td>Muffins or cupcakes baked at 191°C for at least 30 min (containing 2.2 g of egg protein)</td>
<td>83 (43/52)</td>
<td>2.2–18.0 years old, median 7.2 years</td>
<td>Cortot et al. [122]</td>
<td></td>
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<tr>
<td>Muffins baked at 191°C for at least 30 min (containing 2.2 g of egg protein)</td>
<td>66 (66/100)</td>
<td>1.2–19.8 years old, median 5.9 years</td>
<td>Lieberman et al. [123]</td>
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<tr>
<td>Muffin, omelet, hard-boiled egg, soft-boiled egg, or egg cooked by other techniques chosen by parents (containing 3.3 g of egg protein or more)</td>
<td>77 (47/61)</td>
<td>13–40 months, median 19.4 months</td>
<td>Miceli Sopo et al. [124]</td>
<td></td>
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<tr>
<td>Milk</td>
<td>Baked milk challenge with cupcake baked at 176°C for 30 min (containing 1.3 g of milk protein)</td>
<td>76 (37/49)</td>
<td>1.4–4 years old, median 2 years</td>
<td>Sirin Kose et al. [125]</td>
</tr>
<tr>
<td>Muffin baked at 176°C for 30 min (containing 2.8 g of milk protein)</td>
<td>50 (11/22)</td>
<td>4.8–13.9 years old, median 8.4 years</td>
<td>Barbosa et al. [106]</td>
<td></td>
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<tr>
<td>Muffin baked at 176°C for 30 min (containing 1.3 g of milk protein)</td>
<td>74 (65/88)</td>
<td>0.7–6.3 years old, median 3.1 years</td>
<td>Kim et al. [126] [97]</td>
<td></td>
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<tr>
<td>Muffin or cupcake baked at 176°C for 30 min (containing 1.3 g of milk protein)</td>
<td>83 (29/35)</td>
<td>3.1–18.1 years old, median 8.1 years</td>
<td>Bartnikas et al. [127]</td>
<td></td>
</tr>
<tr>
<td>Muffin baked at 180°C for 20 min (containing 0.5 g of milk protein)</td>
<td>73 (51/70)</td>
<td>2.5–9.6 year old, median 5.3 years</td>
<td>Mehr et al. [128]</td>
<td></td>
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<tr>
<td>Shortbread cookie containing 168.6 mg of milk protein</td>
<td>67.2 (43/64)</td>
<td>2–16 years old, median 4.8 years</td>
<td>Gruzelle et al. [129]</td>
<td></td>
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<tr>
<td>Baked milk challenge with muffin baked at 176°C for 30 min (containing 1.3 g of milk protein) Fermented milk challenge with yogurt (containing 8–10 g of milk protein)</td>
<td>For the 32 patients who reacted to unheated milk during an OFC, 38 (12/32) tolerant to yogurt, and 91 (29/32) tolerant to muffin</td>
<td>7–24 months, median 14 m</td>
<td>Uncuoglu et al. [105]</td>
<td></td>
</tr>
<tr>
<td>3 g yogurt from SEK Company (Su’t Endu’stris Kurumu, Istanbul, Turkey)</td>
<td>50 (17/34)</td>
<td>Median 2 years old</td>
<td>Küçükosmanoğlu et al. [94]</td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>Canned tuna</td>
<td>91 (41/45)</td>
<td>Median 9.25 years</td>
<td>Stavroulakis et al. [130]</td>
</tr>
<tr>
<td>90–180 g of canned tuna</td>
<td>100 (45/45)</td>
<td>1.3–30 years old, median 6.0 years</td>
<td>Bernhisel-Broadbent et al. [131]</td>
<td></td>
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</tbody>
</table>

OFC, oral food challenge.
et al. [87], who found that intestinal microbial richness at 3 months of age was associated with an increase in food sensitization at 1 year old; however, this was not true at age of 12 months. In fact, infant feeding guidelines for early food introduction, such as peanut has made corresponding changes [90]. The National Institutes of Allergy and Infectious Diseases recommends that children having severe eczema, egg allergy, or both should introduce peanut into their diet as early as 4–6 months of age under instructions from trained allergy specialists [91]. However, there is some new evidence that the introduction of supplemental foods should be after 6 months old, since the intestinal mucosal barrier in infants is immature, and that the introduction of early solid foods may cause the promotion of allergy rather than tolerance [92]. Whether solid food introduction should be performed before 6 months of age depends on factors, such as food type and nationality, and more research support is needed to draw a conclusion.

**Figure 3.** An overview of the factors that contribute to oral tolerance.

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**Processing Method and Oral Tolerance**

Many allergenic foods were found to present reduced sensitivity after processing. Reported food processing measures that help patients tolerate processed food in clinical trials are listed in Table 1. For some FA subjects, strict avoidance diet is no longer a necessity and their quality of life has improved [93–95]. Certain processing methods can even exert immune-modulatory effects and increase host tolerance to allergenic foods. The 2 allergenic foods under investigation in this field were eggs and milk, and baking was the most common processing method adopted. Today, baked milk and baked egg diets are increasingly used against milk and egg allergy beyond an elimination diet [96].

Egg allergy is one of the most common IgE-mediated FA. Studies have shown that heating can reduce their sensitization, and 55–88% of egg allergy subjects can tolerate baked egg [97–99].

Clinical trials indicated that egg allergy children, who tolerate baked egg have increased possibility to outgrow egg allergy than those intolerate it [100]. To clarify whether intake of baked egg accelerates tolerance to regular egg, an egg elimination diet was introduced to both the baked egg tolerant and intolerant children. Results showed similar tolerance rate to raw egg between the 2 groups, while the control group (egg allergy children tolerant to baked egg and kept daily ingestion) tolerated raw egg with a higher percentage, thus indicating that baked egg consumption can accelerate tolerance to raw egg [101]. Continuous ingestion of extensively heated egg for up to 12 months was found to induce immunological changes that favor tolerance to regular egg, including smaller skin prick test wheal diameters, lower specific IgE level against OVA, and higher specific IgG4 level against both ovomucoid and OVA [102].

Milk allergy is the most common FA in children, with a prevalence of 0.5–3% among 1-year-old children in developed countries, as reviewed by Sackesen [103]. Studies have shown that 50–83% of milk allergy subjects can tolerate baked milk [104–106]. Recently, a randomized controlled trial was performed on 84 egg allergy patients who were baked milk tolerant. Results showed that, at the end of 1 year period, 88.1% of patients who consumed baked milk can tolerate unheated milk, and for those who eliminated milk from diet, the rate was 66.7% (p = 0.018) [107]. The immune-modulatory effect of baked milk on milk allergy patients was also supported by other studies [108–111].

It seems that baked egg and milk are a promising oral immunotherapy for egg and milk allergy patients [113] [112, 113]. In practice, attention should be paid to those baked milk/egg intolerant patients, since anaphylaxis may happen [114]. Moreover, matrix is also important in terms of tolerance induction [115]. However, there are
different voices saying that baked egg/milk tolerance was due to heat-induced conformational change and that no immune-modulatory effect would be observed for the raw ingredient [116]. More data are required for baked egg/milk tolerant participants, who eliminate egg/milk from diet, to compare with baked egg/milk intolerant control or those that randomly consume or avoid baked egg/milk in order to ascertain whether tolerance rate to raw egg/milk differs.

**Conclusion**

The increase in FA prevalence is a direct consequence of reduced tolerance to foods. Early food introduction seems to be a useful measure for higher rate of oral tolerance induction and restoration, including the intestinal mucosal immune defense system, intestinal microbiota, and processing method, among others (shown in Fig 3). Baked milk and egg products showed clinical immune-modulatory effects and function as a promising oral immunotherapy. However, although desensitization to food allergens can be induced, the rate of induced clinical tolerance is low and whether the immune response can rebound is still uncertain.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Xiaotong Yang drafted the manuscript. Rui Liang performed the format editing for submission. Qianlu Xing revised the manuscript. Xiaojuan Ma designed and coordinated the works.

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Oral Tolerance


